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Enoxaparin Anticoagulation Monitoring in the Catheterization Laboratory Using a New Bedside Test

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Objectives This study evaluated the ability of the bedside test Hemochron Jr. Hemonox (International Technidyne Corporation, Edison, New Jersey) to identify patients with insufficient anti-Xa activity level in the catheterization laboratory.

Background Inadequate anticoagulation in patients undergoing percutaneous coronary intervention (PCI) is associated with increased periprocedural ischemic events.

Methods In 296 unselected patients undergoing catheterization and/or PCI, whole blood Hemonox clotting time (CT) and activated partial thromboplastin time (aPTT) were measured at baseline (T1) and 10 min after the intravenous administration of enoxaparin (T2) in patients receiving additional enoxaparin and compared with plasma chromogenic anti-Xa activity level.

Results Median values were 0.1 IU/ml (interquartile range [IQR]: 0.1 to 0.1 IU/ml) and 0.87 IU/ml (IQR: 0.74 to 1.03 IU/ml) for anti-Xa; 74 s (IQR: 70 to 81 s) and 143 s (IQR: 114 to 206 s) for Hemonox CT; and 44 s (IQR: 39 to 50 s) and 72 s (IQR: 58 to 93 s) for aPTT at T1 and T2, respectively. When using Hemonox CT to discriminate patients with anti-Xa level <0.5 IU/ml, the area under the receiver operating characteristic curve was 0.95 ± 0.01 (95% confidence interval [CI]: 0.93 to 0.97) versus 0.89 ± 0.01 (95% CI: 0.86 to 0.92) for aPTT. The threshold value of 120 s was associated with a 94.9% (95% CI: 91.1% to 97.4%) sensitivity and a 73.3% (95% CI: 67.6% to 78.5%) specificity to detect patients with inadequate anti-Xa level (<0.5 IU/ml) and positive predictive and negative predictive values of 73.9% (95% CI: 68.7% to 79.0%) and 94.78% (95% CI: 91.8% to 97.8%), respectively.

Conclusions Hemonox CT appears to be a fast and reliable bedside test for detecting patients insufficiently anticoagulated and needing adjustment of anticoagulation therapy with enoxaparin before PCI. (J Am Coll Cardiol 2010;55:617–25) © 2010 by the American College of Cardiology Foundation

In many countries, low molecular weight heparin (LMWH) enoxaparin is the most common form of heparin used in the treatment of acute coronary syndromes (ACS) (1). Current guidelines from the European Society of Cardiology and other international societies strongly recommend enoxaparin in the treatment of ST-segment elevation myocardial infarction (STEMI) in association with fibrinolysis (Class I, Level of Evidence: A), in the treatment of non–ST-segment elevation ACS for invasive strategy (Class IIa, Level of Evidence: B), and for conservative strategy (Class I, Level of Evidence: B) (2). Additionally, enoxaparin is being evaluated for primary percutaneous coronary intervention (PCI) in STEMI patients (NCT00718471). Recently, the safety and efficacy of intravenous LMWH anticoagulation therapy for patients undergoing either urgent or elective PCI has been demonstrated in a number of trials (3). Compared with unfractionated heparin (UFH), enoxaparin provides more predictive and more stable anticoagulation therapy. In the STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation) trial, target anticoagulation levels were achieved in 86% of patients receiving enoxaparin without monitoring, compared with 20% of

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Abbreviations and Acronyms

ACS = acute coronary syndrome

aPTT = activated partial thromboplastin time

CI = confidence interval

CT = clotting time

IQR = interquartile range

IV = intravenous

LMWH = low molecular weight heparin

MACCE = major cardiovascular and cerebrovascular events

PCI = percutaneous coronary intervention

ROC = receiver-operating characteristic

SQ = subcutaneous

STEMI = ST-segment elevation myocardial infarction

UFH = unfractionated heparin

patients receiving UFH with activated clotting time monitoring, leading to reduced rates of bleeding with enoxaparin (4).

However, many physicians have considered the absence of validated anticoagulation monitoring before catheterization as a limitation to the use of enoxaparin for PCI. Chromogenic anti-Xa activity level is the standard laboratory assay for monitoring the anticoagulant effect of LMWH but is not available at the bedside, and activated clotting time is not discriminant enough for enoxaparin anticoagulation therapy (5). Recently a new, easy to use microcoagulation point-of-care assay, Hemochron Jr. Hemonox (International Technidyne Corporation, Edison, New Jersey), was developed and demonstrated promising results in a small-sized study performed in elective PCI (6).

We decided to evaluate the ability of the Hemonox test to identify patients with an anti-Xa activity level out of the therapeutic range during catheterization and/or PCI, a situation associated with a poor prognosis when measured with the reference chromogenic technique (7,8).

Methods

Patient population. Patients were eligible if all of the following criteria were met: 1) ≥18 years of age; 2) provided signed informed consent; 3) scheduled to undergo elective or urgent cardiac catheterization with possible ad hoc PCI; and 4) had received therapeutic subcutaneous (SQ) doses of enoxaparin or intravenous (IV) bolus of enoxaparin in the catheterization laboratory. Patients were excluded if they had received UFH, warfarin, or any other anticoagulant before catheterization or if they had known bleeding within the past month. The study initially enrolled 313 consecutive patients, of whom 17 were excluded because they did not receive any enoxaparin before or during catheterization (n = 11) or were still receiving vitamin-K antagonist (n = 6) (Fig. 1). Fourteen patients had an unknown anticoagulation status (transfer patients, urgent cases from the emergency department) but were kept in the study as a separate group.

This study was approved by the institutional review board of the Pitié-Salpêtrière Hospital in Paris (CPP), France.

Study design and medication. Study anticoagulation protocol is presented in Figure 2. Patients received upstream SQ enoxaparin treatment before admission to the catheterization laboratory at 1 mg/kg/12 h (patients with normal renal function) or at 0.65 mg/kg/12 h (patients with renal failure defined as creatinine clearance ≤30 ml/min) (9),

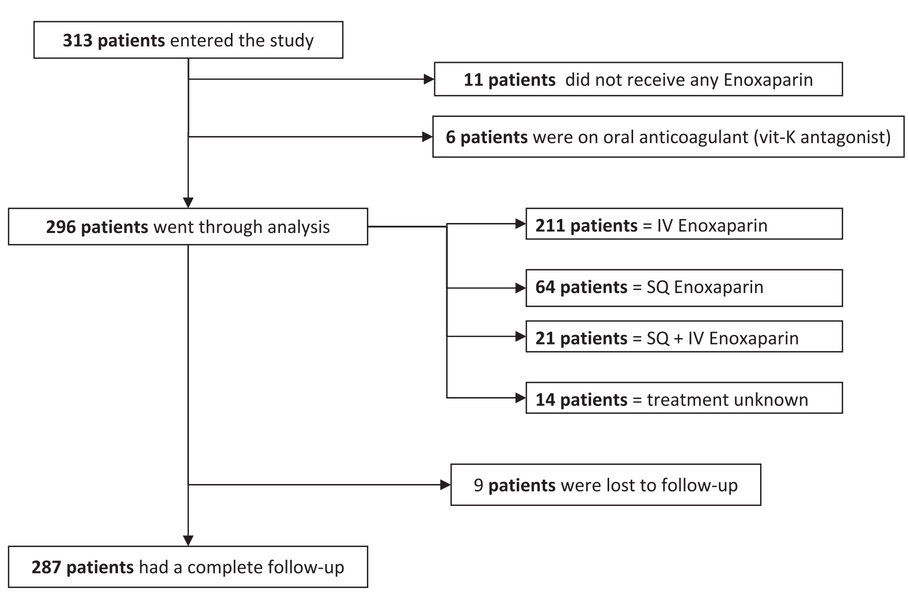

Figure 1 **Flow Chart Representing Operation Clinical Events**

The majority of patients (71.3%) received intravenous (IV) enoxaparin at the dose of 0.5 mg/kg, 21.6% received subcutaneous (SQ) enoxaparin only at the dose of 1 mg/kg/12 h (0.65 mg/kg/12 h in the case of renal impairment), and 7.1% received an additional 0.25 mg/kg IV dose in addition to SQ enoxaparin (last injection between 8 and 12 h). vit-K = vitamin K.

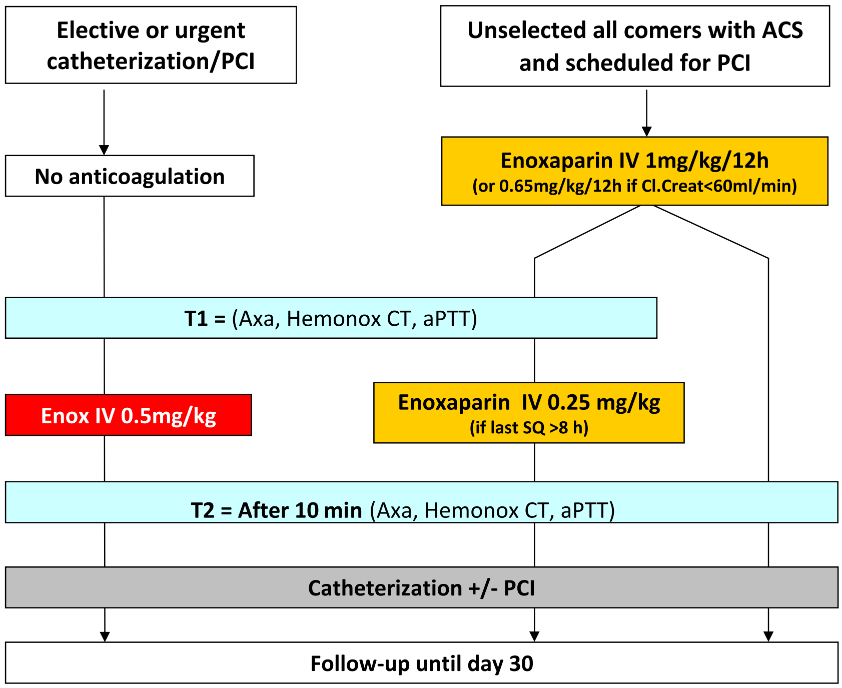

Figure 2 **Study Design**

The first blood sample (T1) was drawn immediately after sheath insertion, and the second draw (T2) was obtained 10 min after the IV enoxaparin (Enox) bolus, if needed, according to the anticoagulation protocol. Patients previously treated with SQ enoxaparin and presenting within 8 h from the last injection had 1 draw (T2) just before percutaneous coronary intervention (PCI), as no additional anticoagulation therapy was administered to these patients. ACS = acute coronary syndrome; aPTT = activated partial thromboplastin time; Axa = anti-Xa activity; Cl Creat = renal clearance of creatinine; CT = clotting time; other abbreviations as in Figure 1.

corresponding to a previously validated (10) dose adjustment for renal failure although slightly different than the Food and Drug Administration recommendation. Patients from this group received no further anticoagulation therapy if the last SQ dose was given within 8 h of the catheterization. An additional 0.25 mg/kg IV bolus was given to patients who had their last SQ enoxaparin dose >8 to 12 h before catheterization. Patients presenting at the catheterization laboratory for elective or urgent/primary PCI who had no prior anticoagulation therapy with enoxaparin or patients with unknown anticoagulation status received a single IV bolus of enoxaparin (0.5 mg/kg) before the procedure. Flush for catheters contained enoxaparin (5 IU/ml) and dipyridamole (40 mg/l). Aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitor use was left to the discretion of the physician in charge of the patient. Catheterization was performed and followed by ad hoc PCI when needed.

Blood samples. Patients without prior anticoagulation therapy and patients presenting 8 to 12 h after the last SQ injection had blood samples drawn from the arterial sheath at 2 different time points for point-of-care (Hemonox and activated partial thromboplastin time [aPTT] tested on fresh whole blood) and chromogenic anti-Xa (tested on plasma) evaluations. The first blood sample (T1) was drawn just after sheath insertion and before the IV bolus, and the second draw (T2) was obtained 10 min after the IV enoxaparin bolus. Patients previously treated with SQ enoxaparin and presenting within 8 h from the last injection had 1 draw just before PCI (T2), as no additional anticoagulation was administered to these patients.

Measurements. The Hemonox clotting time (CT) and aPTT were measured immediately after sampling, using 0.25 ml of blood for each measurement. The remaining 4.5 ml of the blood was collected in Vacutainer tubes (Becton Dickinson, Franklin Lakes, New Jersey) containing trisodium citrate 0.129 mol/l for chromogenic measurement of anti-Xa level. Both Hemonox CT and aPTT were measured at bedside using the Hemochron Jr. Signature + Whole Blood Microcoagulation System with ITC software version 2.2 (International Technidyne Corporation). The Hemonox uses a proprietary lipidated recombinant rabbit brain tissue factor-based reagent (Pel-Freez Corp., Rogers, Arkansas) and formulation buffer, which has been optimized for evaluation of the anticoagulation effect of enoxaparin. A series of light-emitting diode optical detectors aligned with the test channel of the disposable Hemonox cuvette detect the movement of blood in the channel, and its cessation when clotting occurs, and then the instrument reports the whole blood CT value in seconds. The results obtained from this study were for research purposes only and were not taken into consideration in patient management.

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Table 1 Baseline Characteristics

	Study Population (n = 296)
Demographics	
Age, yrs	61.5 ± 13.7
Elderly, age >75 yrs	46 (15.5)
Sex, male	224 (75.7)
Risk factors	
Active smoker	54 (18.2)
Diabetes mellitus	69 (23.3)
Hypertension	167 (56.4)
Dyslipidemia	174 (58.8)
BMI	26.7 ± 4.9
Obesity, BMI >30 kg/m^2	49 (16.5)
Overweight, BMI >25 kg/m^2	118 (39.9)
Creatinine, μM/ml	103.8 ± 71
Creatinine Cl, ml/min	84 ± 39
Renal insufficiency, Cl <60 ml/min	74 (25)
Renal insufficiency, Cl <30 ml/min	12 (4)
Medical history	
ACS	62 (20.9)
Angioplasty	88 (29.7)
Stenting	78 (26.3)
DES	37 (12.5)
CABG	15 (5.1)
Stroke	18 (6.1)
PAD	31 (10.5)
Clinical presentation	
Stable angina or asymptomatic patients	69 (23.3)
Unstable angina	54 (18.2)
NSTEMI, positive troponin	49 (17.4)
STEMI	17 (5.7)
Other	107 (36.1)
Antithrombotic treatment	
ASA	248 (83.8)
Clopidogrel	197 (66.5)
GP IIb/IIIa inhibitor	12 (4.0)
Other medications	
Beta-blocker	188 (63.5)
ACE inhibitor	130 (43.9)
ARAII	60 (20.3)
Lipid-lowering agent	233 (78.7)

Data presented as mean ± SD or n (%).
ACE = angiotensin converting enzyme; ACS = acute coronary syndrome; ARAII = angiotensin II receptor antagonist; ASA = acetylsalicylic acid; BMI = body mass index; CABG = coronary artery bypass graft surgery; Cl = clearance; DES = drug-eluting stent; GP = glycoprotein; NSTEMI = non–ST-segment elevation myocardial infarction; PAD = peripheral arterial disease; STEMI = ST-segment elevation myocardial infarction.

Chromogenic anti-Xa activity measurements were performed on platelet-poor plasma, which was prepared by centrifugation of blood samples at 3,500 *g* for 20 min at 10°C, using the amidolytic assay (CBS 52.44, bovine factor Xa reagents, and STA [simultaneous thermal analyzers], Diagnostica Stago, Parsippany, New Jersey).

The therapeutic range of anti-Xa levels was considered to be between 0.5 and 1.8 IU/ml. The lower limit was based on prior studies of target anti-Xa levels in patients with non–ST-segment elevation ACS (7,11), and in patients undergoing PCI (12–14). The upper value corresponds to the 75th percentile of peak anti-Xa values in patients treated with 1.25 mg/kg every 12 h who did not experience major hemorrhage in the TIMI (Thrombolysis In Myocardial Infarction) 11A study (8).

Clinical follow-up. Thirty-day follow-up was realized through consult and/or telephone interviews. Major cardiovascular and cerebrovascular events (MACCE), including death, stroke, recurrent myocardial infarction, urgent revascularization, and definite and probable stent thrombosis (Academic Research Consortium definition), as well as major and minor bleeding were reported.

Statistical analysis. Categorical variables were expressed as percentages, and continuous variables as mean ± SD and as median with interquartile range (IQR) (25th to 75th percentiles) for biological values (Hemonox CT, aPTT, and anti-Xa). Potential associations between clinical and biological parameters were tested by unvaried procedures using the Mann-Whitney *U* test. Receiver-operating characteristic (ROC) curves were drawn to determine cutoff values of the Hemonox CT as a diagnostic test for monitoring anticoagulation compared with anti-Xa activity levels. We used the Spearman test for nonparametric values to calculate correlation between biological measurements. All analyses were performed with StatView 5.0 SAS software (SAS Institute, Cary, North Carolina).

Results

The baseline characteristics are shown in Table 1. Details of procedure, angiographic results, and biological results are reported in Table 2. Follow-up was achieved in 97% of patients at 30 days.

Table 2 Procedure Characteristics and Biological Measurement at T1 and T2

	Study Population (n = 296)
Angiography	
Nonsignificant lesion or normal angiogram	142 (47.9)
Patients with at least 1 significant lesion	157 (52.1)
Revascularization	
CABG (arterial or saphenous graft)	4 (1.3)
PCI/stenting	165 (55.7)
Anticoagulation and biology, min	
Time sheath insertion to T1	6.3 (3.8)
Time T1 to T2	11.5 (7.1)
Biological measurement	
Hemonox CT T1, s (n = 229)	74 [70–81] (58–444)
Hemonox CT T2, s (n = 289)	143 [114–206] (57–749)
Anti-Xa activity T1, IU/ml (n = 219)	0.1 [0.1–0.1] (0.1–0.96)
Anti-Xa activity T2, IU/ml (n = 269)	0.87 [0.74–1.03] (0.1–1.9)
aPTT T1, s (n = 225)	44 [39–50] (20–136)
aPTT T2, s (n = 288)	72 [58–93] (20–400)

Values are n (%) or median [interquartile range] (minimum–maximum).
aPTT = activated partial thromboplastin time; CABG = coronary artery bypass graft surgery; CT = clotting time; PCI = percutaneous coronary intervention; T1 = time point 1; T2 = time point 2.

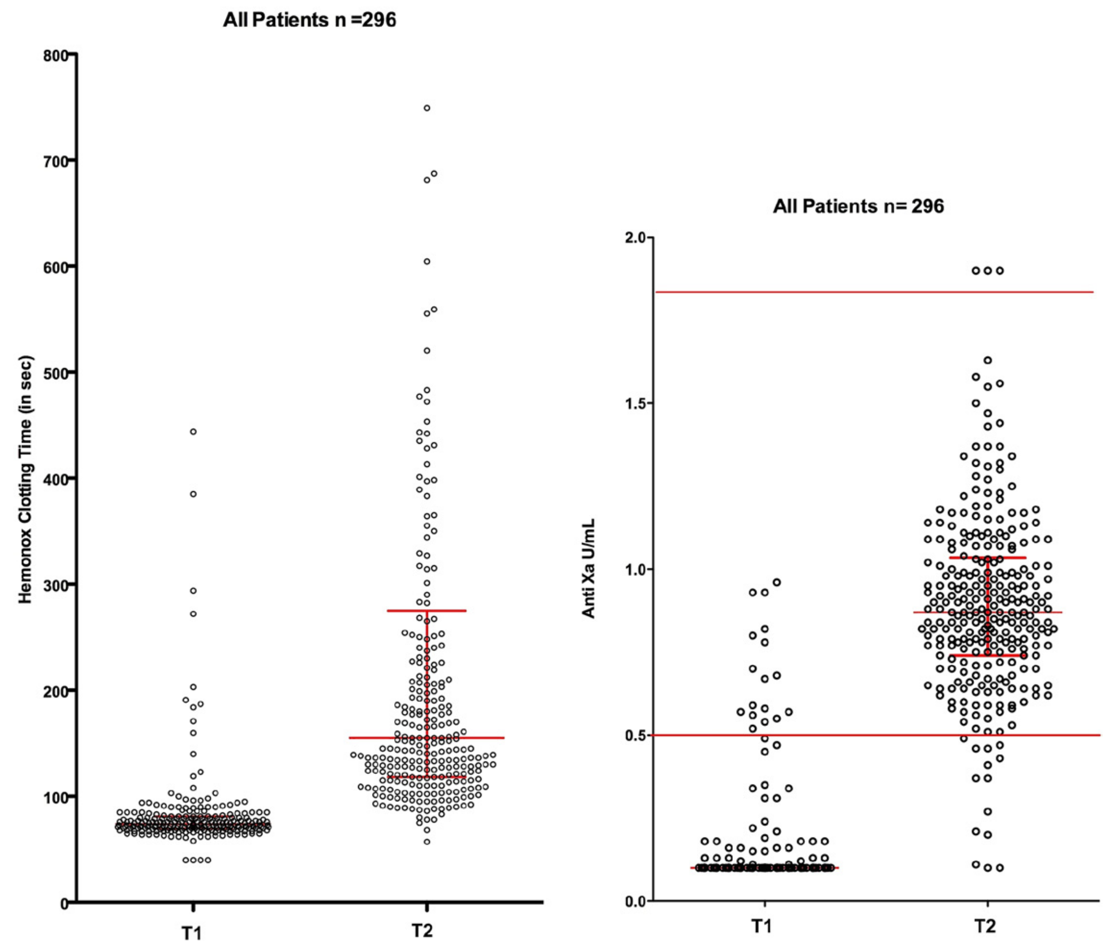

Figure 3 **Biological Data**

(Left) Hemonox clotting time distribution at time 1 (T1) and time 2 (T2). **Horizontal red bars** represent median and interquartile range. Out-of-range high (n = 36) and out-of-range low values (n = 4) were not represented on the graph. **(Right)** Anti-Xa activity level at T1 and T2. **Horizontal red bars** represent median and 75th and 25th percentiles (interquartile range). The **bottom red line** represents 0.5 IU/ml, and the **top red line** represents 1.8 IU/ml.

Baseline analysis and distribution of anti-Xa levels. The distribution of anti-Xa levels is represented in Figure 3, left panel. The anticoagulation protocol led to optimal anticoagulation in 95% of patients just before catheterization/PCI (T2). Only 14 patients (5.2%) had insufficient anticoagulation (median anti-Xa = 0.32 IU/ml; IQR: 0.17 to 0.47 IU/ml), with 1 patient in the SQ plus IV group, 7 in the IV-only group, and 6 in the SQ-only group. Over-anticoagulation, defined as an anti-Xa level >1.8 IU/ml, occurred only in 3 patients (1%) who all had an anti-Xa level of 1.9 IU/ml. These 3 patients already had baseline anti-Xa activity >0.5 IU/ml. The median anti-Xa levels of patients with an unknown anticoagulation status before catheterization (n = 14, transfer patients with limited chart information) and who received a single IV bolus of enoxaparin (0.5 mg/kg) were 0.65 IU/ml (IQR: 0.44 to 0.86 IU/ml) at T1 and 1.14 IU/ml (IQR: 0.78 to 1.50 IU/ml) at T2, suggesting that most of them probably received some anticoagulation therapy before admission and T1 blood sampling.

Baseline analysis and distribution of Hemonox CT. Distribution of Hemonox CT is represented in Figure 3, right panel. Median Hemonox CT was 74 s (IQR: 70 to 81 s) at baseline (T1) and 143 s (IQR: 114 to 206 s) at T2. Forty measurements (7.7%) were categorized as out-of-range by the Hemonox test; of those, 36 measurements yielded "out of range high" results and 4 yielded "out of range low" results, which may indicate results outside the upper and lower limits of the assay range. These values were kept in the analysis and were used as categorical variables for the calculation of ROC curves. Among the 36 out-of-range high values, 34 (94.4%) corresponded to patients with anticoagulation level >0.5 IU/ml, and all the out-of-range low values corresponded to patients with anti-Xa level <0.5 UI/ml.

Relative response to IV enoxaparin. Anti-Xa level and Hemonox CT were increased by 0.75 IU/ml (mean value between T1 = 0.14 IU/ml and T2 = 0.89 IU/ml) and 106 s (mean value between T1 = 73 s and T2 = 179 s), respectively,

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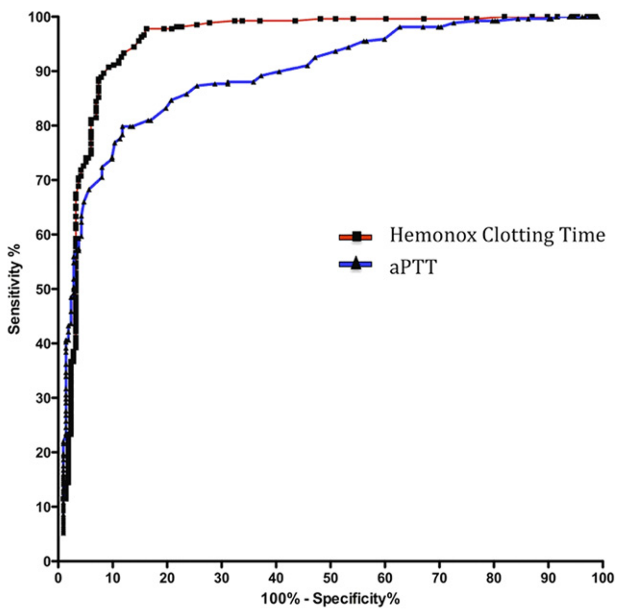

Figure 4 **ROC Curves**

Receiver-operating characteristic (ROC) curves for Hemonox clotting time in **red** and activated partial thromboplastin time (aPTT) in **blue** for detection of patients with anti-Xa level <0.5 IU/ml using the Chromogenic assay as reference.

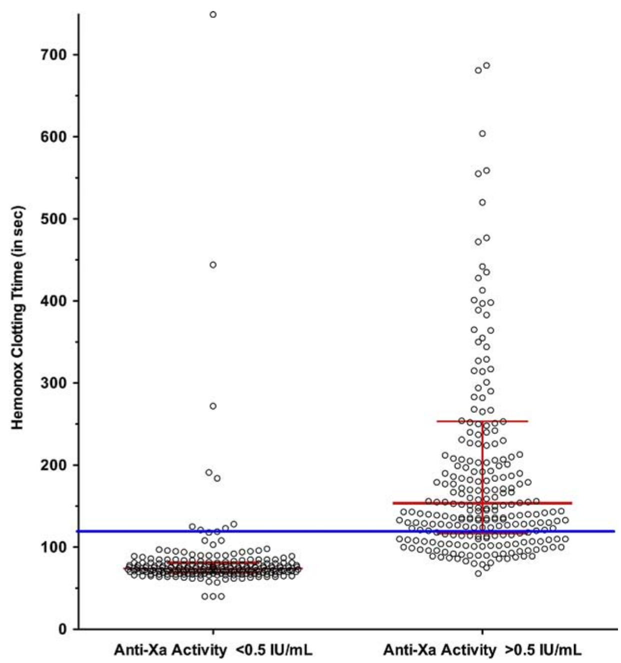

Figure 5 **Distribution of Hemonox CT**

The **blue line** indicates a threshold of 120 s, identifying patients with anti-Xa activity <0.5 IU/ml with a sensitivity of 94.9% and a specificity of 73.9% when the Hemonox clotting time is <120 s (positive test to identify patient with inadequate level of anticoagulation). The **horizontal red bars** indicate median and interquartile range.

when a 0.5 mg/kg IV bolus of enoxaparin was given. In patients who received SQ enoxaparin and needed an additional 0.25 mg/kg IV bolus of enoxaparin, anti-Xa level and Hemonox CT increased by 0.64 UI/ml (mean value between T1 = 0.32 IU/ml and T2 = 0.96 IU/ml) and 178 s (mean value between T1 = 86 s and T2 = 254 s), respectively.

Evaluation of the biological test. The correlation between anti-Xa levels and Hemonox CT was stronger than the correlation between anti-Xa levels and aPTT, whether analyzed on the global T1 and T2 values ($r = 0.81$, 95% confidence interval [CI]: 0.77 to 0.84, $p < 0.0001$ vs. $r = 0.62$, 95% CI: 0.56 to 0.68, $p < 0.0001$) or separately on T1 ($r = 0.45$, 95% CI: 0.33 to 0.55, $p < 0.0001$ vs. $r = 0.17$, 95% CI: 0.036 to 0.31, $p < 0.01$) and T2 values ($r = 0.39$, 95% CI: 0.27 to 0.49, $p < 0.0001$ vs. $r = 0.0085$, 95% CI: −0.11 to 0.13, $p < 0.89$). The ROC curves were calculated for Hemonox CT and aPTT using the chromogenic measurements of anti-Xa levels as the reference method to discriminate anti-Xa levels <0.5 IU/ml from those ≥0.5 IU/ml (Fig. 4). When comparing all Hemonox CT values with corresponding anti-Xa levels, the area under the curve was higher for Hemonox CT (0.95 ± 0.01, 95% CI: 0.93 to 0.97, $p < 0.0001$; 486 values) than the bedside measurements of aPTT (0.89 ± 0.01, 95% CI: 0.86 to 0.92, $p < 0.0001$; 480 values); results were confirmed by the Delong & Delong nonparametric test, with a difference of 0.06 (95% CI: 0.03 to 0.09, $p < 0.0001$).

Table 3 **Sensitivity, Specificity, Likelihood Ratio, PPV, and NPV**

Hemonox CT, s	Sensitivity	Specificity	Likelihood Ratio	PPV	NPV
<120	94.9 (91.1–97.4)	73.3 (67.6–78.5)	3.5	73.9 (68.7–79.0)	94.8 (91.8–97.8)
<110	94.0 (89.9–96.8)	78.9 (73.5–83.6)	4.4	78.0 (72.9–83.0)	94.3 (91.3–97.3)
<105	93.1 (88.8–96.1)	83.3 (78.3–87.6)	5.6	81.6 (76.8–86.4)	93.8 (90.8–96.8)
<100	92.6 (88.2–95.7)	88.2 (83.7–91.8)	7.8	86.2 (81.8–90.6)	93.8 (90.8–96.7)
<95	89.8 (85.0–93.5)	91.1 (87.1–94.2)	10.1	89.0 (84.8–93.1)	91.9 (88.6–95.1)
<90	86.1 (80.8–90.4)	94.4 (91.0–96.9)	15.5	92.5 (88.9–96.2)	89.5 (86.0–93.1)
<85	83.8 (78.2–88.4)	97.8 (95.2–99.2)	37.7	96.8 (94.2–99.3)	88.4 (84.8–92.0)
<80	74.5 (68.2–80.2)	98.5 (96.2–99.6)	50.3	97.6 (95.2–99.9)	83.0 (78.9–87.1)

Values are % (95% confidence interval) unless otherwise noted. Sensitivity, specificity, likelihood ratio, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each threshold of Hemonox clotting time (CT) to detect patients with an anti-Xa activity <0.5 IU/ml. PPV indicates the probability of having a positive test (Hemonox CT <120 s) when the anti-Xa activity is <0.5 IU/ml. NPV indicates the probability of having a negative test (Hemonox CT >120 s) when the anti-Xa activity is >0.5 IU/ml.

Detection of patients with insufficient anticoagulation therapy. The main purpose of a bedside test is the ability to rapidly measure the level of anticoagulation and identify patients who are insufficiently anticoagulated with enoxaparin at the time of PCI. We looked for the Hemonox CT threshold value having the best performance, especially in terms of sensitivity to identify patients with an anti-Xa activity <0.5 UI/ml. Different threshold values were evaluated and are presented in Table 3. A threshold value of 120 s was associated with a 94.9% sensitivity (95% CI: 91.1% to 97.4%) and a 73.3% specificity (95% CI: 67.6% to 78.5%), with a likelihood ratio of 3.5 and an overall 83% (95% CI: 80% to 86%) accuracy to detect patients with inadequate anti-Xa level (<0.5 IU/ml) (Fig. 5). With this threshold, the positive and negative predictive values of Hemonox CT as a diagnostic test were 73.9% (95% CI: 68.7% to 79.0%) and 94.78% (95% CI: 91.8% to 97.8%), respectively. A lower threshold value of 100 s improved specificity to 88.2% (95% CI: 83.7% to 91.8%), with a modest reduction of sensitivity of 92.6% (95% CI: 88.2% to 95.7%) and a likelihood ratio of 7.8 to detect patients with inadequate anti-Xa level (<0.5 UI/ml). With this threshold, the positive and negative predictive values were 86.2% and 93.8%, respectively.

Special populations. Obese patients (body mass index >30 kg/m^2; n = 49 [16.5%]), exhibited higher levels of anti-Xa as compared with their nonobese counterparts (n = 247 [83.5%], 0.98 IU/ml [IQR: 0.84 to 1.15 IU/ml] vs. 0.86 IU/ml [IQR: 0.72 to 1.00 IU/ml], p = 0.0017). Similarly, Hemonox CT was higher in obese patients than in nonobese patients (172 s [IQR: 120 to 364 s] vs. 139 s [IQR: 113 to 194 s], respectively; p = 0.019). Patients with renal impairment (creatinine clearance <60 ml/min; n = 46 [15.5%]) had lower anti-Xa level than patients with creatinine clearance >60 ml/min (n = 250 [84.5%], 0.82 IU/ml [IQR: 0.67 to 0.95 IU/ml] vs. 0.9 IU/ml [IQR: 0.77 to 1.08 IU/ml], respectively; p = 0.006), and no difference in Hemonox CT values (144 s [IQR: 114 to 191 s] vs. 139 s [IQR: 113 to 210 s], respectively; p = 0.9). In patients with severe renal impairment (creatinine clearance <30 ml/min), anti-Xa level was 0.66 IU/ml (IQR: 0.57 to 1.06 IU/ml) versus 0.87 IU/ml (IQR: 0.75 to 1.03 IU/ml) in patients with creatinine clearance >30 ml/min (p = 0.12). Similarly, Hemonox CT was 148 s (IQR: 112 to 292 s) versus 154 s (IQR: 118 to 271 s, p = 0.8), respectively.

In elderly patients (>75 years of age; n = 74 [25%]), anti-Xa level and Hemonox CT values were similar to those observed in younger patients (n = 222 [85%]; 0.84 IU/ml [IQR: 0.72 to 1.06 IU/ml] vs. 0.88 IU/ml [IQR: 0.74 to 1.02 IU/ml], p = 0.86; and 133 s [IQR: 108 to 191 s] vs. 143 s [IQR: 116 to 211 s], p = 0.32, for anti-Xa and Hemonox CT, respectively).

Clinical outcomes and safety. Among the 287 patients who completed the follow-up, 3 died (1.0%) and 13 (4.5%) experienced an MACCE. Anti-Xa level was 0.76 IU/ml (IQR: 0.55 to 1.07 IU/ml) versus 0.87 IU/ml (IQR: 0.74 to 1.03 IU/ml, p = 0.3) and Hemonox CT was 157 s (IQR: 100 to 21 s) versus 139 s (IQR: 113 to 200 s, p = 0.9) in patients with (n = 13) versus without (n = 274) MACCE at 30 days, respectively.

Bleeding rate was low, with 2 major bleedings (0.66%); both patients had an anti-Xa level <1.2 IU/ml. Among the 3 patients who died, 1 had a borderline anti-Xa level of 0.46 IU/ml (the respective Hemonox CT was 95 s), the second had an anti-XA level of 0.6 IU/ml (the respective Hemonox CT was 140 s), and the third had an unknown anti-Xa value at T2 but Hemonox CT was 78 s.

Discussion

The main purpose of a LMWH enoxaparin bedside test is the ability to rapidly and reliably monitor enoxaparin anticoagulation therapy in patients managed with SQ doses who transit to PCI or in patients receiving IV bolus during cardiac interventional procedure, and ensure that patients receive adequate anticoagulation therapy before the start of the procedure. Thus, the sensitivity of the bedside test is critical. We demonstrate in this report that enoxaparin-treated patients with inadequate anti-Xa activity (<0.5 IU/ml) can be accurately and easily identified by the Hemonox bedside test, with a high sensitivity (94.9%) when using a 120 s threshold. This threshold allows clinicians to rule out the need for additional anticoagulation therapy when levels are beyond 120 s, with a good negative predictive value (94.8%). The ROC curves and the good correlation between Hemonox CT and the anti-Xa level measured with the chromogenic method confirm the accuracy of this bedside test in the whole range of values obtained in our population. In contrast, and not surprisingly, bedside aPTT measurement was less sensitive.

Despite increasing evidence on the equivalent efficacy and superior safety of enoxaparin as compared with UFH, enoxaparin is still not widely used in patients undergoing PCI (3). The inability to rapidly monitor the anticoagulant effect of enoxaparin in a similar fashion as the activated clotting time with UFH has limited the use of enoxaparin in interventional cardiac procedures. This study demonstrates that Hemonox is a suitable bedside test and is easy to use in the catheterization laboratory for monitoring the anticoagulation level of enoxaparin in patients undergoing PCI.

Several studies have shown that an SQ upstream treatment by enoxaparin at the dose of 1 mg/kg twice daily (0.65 mg/kg twice daily for patients with impaired renal function) allows adequate anticoagulation for PCI within 8 h of the last injection, whereas an additional IV bolus of 0.25 to 0.30 mg/kg is needed (13,15,16) if the last SQ was injected more than 8 h and less than 12 h before the procedure. Our work confirms that this enoxaparin dose regimen is associated with an anti-Xa activity in the therapeutic range (0.5 to 1.8 IU/ml) in the large majority of patients (95%) with low rates of under- or over-anticoagulated patients (4% and 1%, respectively). However, patients undergoing PCI with an anti-Xa activity <0.5 IU/ml may be at high risk of ischemic complications. Only a few studies have been conducted with sufficient power to assess correlations between target anti-Xa levels and outcomes of ischemic complications (17,18). A recent study involving unstable angina/non-STEMI patients reported a 3-fold increase in 30-day mortality associated with suboptimal anticoagulation (anti-Xa levels <0.5 IU/ml) (7). Such findings suggest the need for monitoring anti-Xa activity with a rapid point-of-care test to identify the patients who require dose adjustment.

Our Hemonox results are in agreement with those reported from previous studies conducted on a small sample size (5,6). Additionally, the study was conducted in a population treated exclusively with enoxaparin and included special patient groups such as patients with renal failure, the elderly, and obese patients. The absence of over-anticoagulation therapy for these specific patient populations shows the effectiveness of the protocol used and confirms previous results (19). Nevertheless, results from this study suggest the utility of the point-of-care test in monitoring enoxaparin in special patient.

Because the main objective of the monitoring test is its level of sensitivity for defining patients who are under-anticoagulated, the threshold of 120 s may be recommended, especially in patients at high risk of thrombosis. In other words, if Hemonox CT is <120 s in the catheterization laboratory, an additional IV enoxaparin bolus of 0.5 mg/kg could be given to the patient before PCI to ensure achieving an effective anti-Xa level within the therapeutic range (0.5 to 1.8 IU/ml). Our results indicate that for patients without any prior anticoagulation, an IV enoxaparin bolus of 0.5 mg/kg yields an average anti-Xa activity level of 0.73 IU/ml. Thus, patients with a Hemonox CT value <120 s but with some residual anti-Xa activity (<0.5 IU/ml) would not be over-anticoagulated with an additional IV bolus (15). Actually, we observed this scenario in a few patients of our study whose anticoagulation status was unknown at the time of catheterization; they received an IV bolus of 0.5 mg/kg and remained within the recommended therapeutic range of anti-Xa level.

A more graded approach to Hemonox CT could be used; lower cutoff values (100 s) would increase specificity, which may be useful in stable patients and/or patients at high risk of bleeding; additional IV enoxaparin doses <0.5 mg/kg could also be used in patients with Hemonox CT 80 to 120 s.

All these strategies would have to be tested prospectively in further studies as well as the value of bedside enoxaparin monitoring in situations such as STEMI patients treated with fibrinolytic drugs or anticoagulation therapy during hemodialysis.

In daily practice, the Hemonox test may be used in the catheterization laboratory to assess the appropriate level of anticoagulation therapy in patients undergoing PCI and to avoid the use of UFH in addition to enoxaparin, as is still done by some interventionists and has been shown to be associated with worse outcome in the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial (20).

Study limitations. One important limitation of our study is that it was not powered to assess the impact of the Hemonox CT on clinical outcomes. Another limitation is the limited information obtained on high levels of anticoagulation, as very few patients in our population reached anti-Xa values >1.8 IU/ml. Finally, the cost effectiveness of a monitoring-guided strategy of enoxaparin anticoagulation therapy remains to be established.

Conclusions

According to the results of this study, Hemonox CT appears to be a fast and reliable bedside test that can be used to monitor enoxaparin anticoagulation therapy immediately before catheterization and PCI.

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